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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,454	12/13/2006	Timothy Vollmer	68682-PCT-US/JPW/JW	1309
23432 7590 04/13/2010 COOPER & DUNHAM, LLP 30 Rockefeller Plaza 20th Floor NEW YORK, NY 10112				
EXAMINER AUDET, MAURY A				
ART UNIT		PAPER NUMBER		
1654				
MAIL DATE		DELIVERY MODE		
04/13/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/556,454

Applicant(s)

VOLLMER, TIMOTHY

Examiner

MAURY AUDET

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 3/29/10.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-13, 19-21, 23-25 and 27-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-13, 19-21, 23-25 and 27-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's amendment, RCE are acknowledged. Applicant has amended claim 1 to change the timeframe of administration from "periodically" to "substantially preceding":

1. (Currently Amended) A method of treating a subject afflicted with a form of multiple sclerosis comprising ~~periodically~~ administering to the subject an amount of glatiramer acetate and an amount of mitoxantrone, wherein the administration of the mitoxantrone substantially precedes the administration of the glatiramer acetate, and wherein such administration is the amount when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject.

However, there is no definition found in the specification for what is contemplated by the *claimed invention's* "substantially precedes", which was an alternative embodiment described. Thus, the metes and bounds of the claimed invention are unclear (raising a new rejection under 35 USC 112 2nd). Notwithstanding this side issue, the *In re Kerkhoven* fact pattern remains in the claims (administering two known products for their known use, together), and the 35 USC 103 rejection is maintained below; absent evidence to the contrary of test data showing administering mitoxantrone at some "substantially preceding" time before glatiramer acetate produces unexpected results in 1 or more MS symptoms v. a control group where both compounds are administered at/about the same time.

As noted previously, the present application is a 371 National Stage entry of PCT/US04/15225, in which this Examiner also prepared both the Search & Written Reports (Forms 210 and 237 respectively) on the identical claims 1-25. The latter found that the invention, although finding Novelty under PCT Article 33(2), was not deemed to involve an

Inventive Step under PCT Article 33(3). The findings therein, are transferred nearby verbatim via the US correlational Statutory Code section 35 USC 103.

Claim Rejections - 35 USC § 112 2nd-New

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-13, 19-21, 23-25, and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In e.g. claim 1, there is no definition found in the specification for what is contemplated by the *claimed invention's* "substantially preceding", which was an alternative embodiment described. Thus, the metes and bounds of the claimed invention are unclear (raising a new rejection under 35 USC 112 2nd). The only recitation to the newly added amendment is an alternative embodiment with no description of how much time (minutes, days, weeks, months, years?) before mitoxantrone is to administered "substantially preceding" glatiramer acetate:

[0036] In a further embodiment, the administration of the glatiramer acetate substantially precedes the administration of the mitoxantrone.

[0037] In an added embodiment, the administration of the mitoxantrone substantially precedes the administration of the glatiramer acetate.

Applicant's, on page 7-8 of the response, rely on the following to assert what is to be meant by "substantially precedes":

Example 1 which discloses the details of the treatment regimen i.e., IV infusion of **mitoxantrone at months 0, 1 and 2 followed by daily subcutaneous injections of glatiramer acetate two weeks after the last scheduled infusion of mitoxantrone.**

Contrary the Applicant's assertion, the still open, broadly claimed invention is not claimed commensurate in scope with e.g. Example 1 above.

Below, the 103 rejection is maintained that the use of mitoxantraone and glatiramer acetate, alone (which is really what the method is now, since "substantially precedes" could mean any time frame before of the former before the latter) or in combination, for MS treatment, is known - and predictable that would be additive or synergistic for one or more symptoms (based on the PTO view of using known substances for known functions, as opposed to what Applicant has described as the FDA view).

Based on Applicant's response, the method Applicant seems to have described would appear more like the following, based on Ex. 1 above and the Vollmer article results noted on page 8 of the response (assuming support is present in the specification for things like 'accelerating' and 'enhancing' or the like):

"A method of accelerating and enhancing the efficacy of glatiramer acetate (GA) in reducing Gd-enhancing lesions and relapse in an MS patient in need thereof, by first administering mitoxantrone by IV 1 or 2 months before GA, followed by daily SC injections of GA two weeks after the last scheduled infusion of mitoxantrone."

Based on the test results described, the Examiner is uncertain as to how much further the scope (e.g. breadth) of the invention could be extended beyond the above, based on the art of record.

Claim Rejections - 35 USC § 103-Maintained

The invention is drawn to the composition and method of treating a subject afflicted with multiple sclerosis with the combination of active agents glatiramer acetate and mitoxantrone; wherein the latter is now to be administered “substantially preceding” the former.

The rejection of claims 1-4, 6-13, 19-21, 23-25, and 27-29 under 35 U.S.C. 103(a) as being unpatentable over Szabo et al (US 6,531,464) in view of Arnon et al. (US 6,214,791) and Kerwar et al. (US 4,617,319), is maintained for the reasons of record. Applicant’s arguments have been considered but are not found persuasive. The *In re Kerkhoven* fact pattern remains in the claims (administering two known products for their known use, together), and the 35 USC 103 rejection is maintained below; **absent evidence to the contrary of test data showing administering mitoxantrone at some “substantially preceding” time before glatiramer acetate produces unexpected results in 1 or more MS symptoms v. a control group where both compounds are administered at/about the same time.** Without this, either *In re Kerkhoven* applies that administration of known agents for a known use, in combination (even if not at the exact same time) would have predictable results OR since the agents are NOT actually being administered at the same time, then they are simply being separately administered, as the art already teaches both for (bordering on a 102 rejection based on the art record).

The rejection and previous reply in the pre-RCE I. Final Rejection and II. Advisory Action & Pre-Interview are copied below for continuity of record:

Applicant, in his 105 page response, including numerous MPEP sections and case law relevant to KSR/obviousness standards, essentially relies on MPEP section 2143.02, in his Section 5 Exhibit, which cites that:

2143.02 Reasonable Expectation of Success Is Required [R-6] -2100 Patentability

2143.02 Reasonable Expectation of Success Is Required [R-6]

A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. m., ~, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

I. OBVIOUSNESS REQUIRES ONLY A REASONABLE EXPECTATION OF SUCCESS

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (Claims directed to a method of treating depression with amitriptyline (or nontoxic salts thereof) were rejected as *prima facie* obvious over prior art disclosures that amitriptyline is a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess antidepressive properties, in view of prior art suggesting the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement and because a research paper comparing the pharmacological properties of these two compounds suggested clinical testing of amitriptyline as an antidepressant. The court sustained the rejection, finding that the teachings of the prior art provide a sufficient basis for a

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reasonable expectation of success.); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims were directed to a process of sterilizing a polyolefinic composition with high-energy radiation in the presence of a phenolic polyester antioxidant to inhibit discoloration or degradation of the polyolefin. Appellant argued that it is unpredictable whether a particular antioxidant will solve the problem of discoloration or degradation. However, the Board found that because the prior art taught that appellant's preferred antioxidant is very efficient and provides better

results compared with other prior art antioxidants, there would have been a reasonable expectation of success.).

II. AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED; APPLICANTS MAY PRESENT EVIDENCE SHOWING THERE WAS NO REASONABLE EXPECTATION OF SUCCESS

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success.); *In re O'Farrell*, 853 F.2d 894, 903,

7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

III. PREDICTABILITY IS DETERMINED AT THE TIME THE INVENTION WAS MADE

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986) (Although an earlier case reversed a rejection because of unpredictability in the field of monoclonal antibodies, the court found "in this case at the time this invention was made, one of ordinary skill in the art would have been motivated to

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produce monoclonal antibodies specific for human fibroblast interferon using the method of [the prior art] with a reasonable expectation of success." 3 USPQ2d at 1016 (emphasis in original).).

; to support his primary position, on page 4-5 of the response that:

"Yet furthermore, applicant has made the unexpected observation that immunosuppression with mitoxantrone accelerates and enhances the efficacy of glatiramer acetate administered to the patient (see instant claim 29; page 15, lines 15-18 of the subject application; and page 2, 2nd column, last full paragraph and page 7, 2nd column, last paragraph ending on page 8 of Vollmer et al.).

In addition, the enhancement of glatiramer acetate treatment is demonstrated by a significant reduction in both the accumulation of Gd-enhancing lesions and in the mean relapse rate (see instant claims 26-28 and Vollmer et al., page 5, bottom of 2nd column to page 6, 2nd column, first full paragraph).

The prior art provides no evidence or even suggestion that treatment with mitoxantrone would enhance the efficacy of glatiramer acetate in general or by reducing the accumulation of Gd-enhancing lesions or mean relapse rate."

The Examiner counters, based on Szabo et al.'s teaching of this combination from a list of 5 MS agents, that the presumption by one of ordinary skill in the art of using two known compounds for MS, in combination, is that 1 or the other would only enhance the other, and thereby provide some degree of additive, if not synergistic effect. Hence, the teachings of Szabo et al. in the first place, to even contemplate their combined therapeutic use for MS.

Applicant on page 3 of the response attempts to disqualify Szabo et al.'s combination teaching, citing the Examiner's interpretation as erroneous; however, the Examiner counters that

Applicant's Attorney has misinterpreted the "qualifying" language present in Szabo et al.

Applicant states:

Initially, the Examiner has misinterpreted claims 10 and 11 of Szabo et al. Specifically, these claims cannot be interpreted to disclose a combination treatment of glatiramer acetate and mitoxantrone. A proper construction of claim 11 indicates a disclosure of only one member of the group. This is well settled patent law. See, e.g. *Abbott Laboratories v. Baxter Pharmaceutical Products, Inc.*, 334 F.3d 1274, 1281, 67 USPQ2d 1191, 1196 (Fed. Cir.2003), attached hereto as Exhibit 1 holding that 'a' with 'consisting of' in this case indicates only one member of a Markush group. See *KJC Corp.*, 223 F.3d at 1356. If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim." **Claim 11 of Szabo et al. clearly fails to recite any qualifying language and, thus, clearly fails to support the Examiner's erroneous construction. In fact, claim 11 of Szabo et al. requires that no more than one member from the group is to be selected for administration.** Accordingly, the prior art fails to teach or suggest combining mitoxantrone and glatiramer acetate for treatment of multiple sclerosis.

Claims 10 and 11 of Szabo et al. expressly teach:

10. The method of claim 1, further comprising administering one or more additional agents for treating symptoms associated with multiple sclerosis.

11. The method of claim 10, wherein the second agent is selected from the group consisting of a glucocorticoid, an interferon, glatiramer acetate, immunoglobulin, and mitoxantrone.

The 5 "one or more additional agents" recited in claim 11 are the expressly contemplated one or additional agents. The 'or more' language removes Abbott as an analogous caselaw fact pattern because Szabo et al. must be read in light of itself and all claims to which it depends, which

means the 'or more' does not somehow make the Markush group 'consisting of' language limited to only 1 agent.

Furthermore, as the second case cited, the 'or more' language IS the qualifying language that removes the present fact-pattern applying Szabo et al. from analogy with the KJC Corp. case that Applicant's Attorney has cited. Wherein, although the facts of KJC Corp were not fully provided the Examiner, it can only be presumed there was no such qualifying language latter, as is present in the Szabo et al. claim 10/11.

Applicant's Attorney is reminded that dependent claims are read as having ALL of the limitations of any claim to which they depend, thus the qualifying language of claim 10 to be read not separate from claim 11, but as fully encompassed by claim 11. Read this way, claim 11 actually reads:

11. The method of claim 1, further comprising administering one or more additional agents for treating symptoms associated with multiple sclerosis, wherein the second agent is selected from the group consisting of a glucocorticoid, an interferon, glatiramer acetate, immunoglobulin, and mitoxantrone.

Thus, the literal meaning of 'or more' in claim 11 (not 10), can only mean that the 'more' than 1 additional agent, must be selected from the group of 5 agents in claim 11. The fact that claim 11 recites this group of 5 (as 1 'or more' that may be coadministered) in proper Markush claim format using "consisting of" does not, as Applicant's Attorney has improperly interpreted the claim, mean that 'only 1' of those agents can be selected, based on the 'consisting of' language. If such were the case, this would contradict and cancel out the full scope of claim 11, and the breadth Issued Patentee in the claim 11, **that another 2 – 5 agents, the 'or more' than 1**

claimed, is taught as contemplated for use in the composition thereof, for MS treatment – depending on the symptoms being targeted, and the ability of 1 of more of those agents to target different or target better, certain symptoms of MS.

Continuing this thread, claim 10 and 11 claims that this 'one or more additional agents are for treating symptoms associated with MS'. The reason there are many varied approach to the complex treatment of MS, is that there is no perfect therapy. It is well established that the 2 compounds presently claimed are capable of treating different symptoms of MS and/or the same symptoms but with different levels of success in individual patients – or 1 would trump the other as superior thereby eliminating the value of the other in the pharmaceutical market. Thus, the rationale for 'or more' in claim 10, is that the agents of claim 11 (or other nonclaimed agents) can be administered, based on the desired symptoms to be treated, or use thereof to treat certain symptoms better with one agent or another.

Combination therapy in highly complex disorders such as MS, or even diabetes, is well known in the art.

The Examiner has fully considered the record:

- 1) Applicant's amendment and 105 page response;**
- 2) The Exhibits of Volmer's 2008 article in MS; the MPEP section on 2143.02; the KSR and related caselaw;**
- 3) each in the context of the claimed invention in view of the prior art combination; and can only conclude and maintain, not yet convinced by Applicant's arguments and evidence of record, that based the prior art combination, if not Szabo et al. alone, that**

one of ordinary skill in the art, using two known MS agents in combination (2 of 5 Szabo et al. taught/contemplated), would have had a reasonable expectation of success in treating MS by their combination, satisfying MPEP section 2143.02, as well as the recent case law guidance of and citing KSR.

The real, fundamental issue of the invention as claimed v. the prior art is whether Szabo et al. taught a laundry list of known MS agents that 'could' be selected for combinatorial therapy for MS, or small, "immediately envisaged" (borderline 102 art) for the same? The Examiner is not convinced by Applicant's evidence of record; however, voluminous it may be; that Applicant has removed the art to that of the former (laundry list) from that of what it appears to be (immediately envisaged). A list of 5 agents, and the express teaching (or at a minimum) that any of the 5 therein may be used concurrently in a combination therapy is simply too overwhelming evidence that such would have been predictable, in the form Applicant has presently claimed. Based on the predictable results that both agents presently claimed were known for use as MS treatment agents. Furthermore, Applicant's have claimed ANY form of administration of the two, "periodically" even (claim 1); including administering either agent "substantially preceding" the other (claims 16-17). Either of these limitations, under their broadest 'reasonable' interpretation, could mean days or even months apart of administration times, in combination or in the context of preceding the other. The breadth of this interpretation borders on indefiniteness in the context of what the metes and bounds of the invention really is, in order to carry out it's aim of reducing relapses of MS; and only further raises doubts as to a claimed invention directed to a therapy of known agents in combination for their known use, to somehow elicit something 'unexpected' (beyond merely synergistic effect, which would naturally be

expected by administering two agents in combination, as Szabo et al. taught/suggested) - when the administration thereof is claimed essentially as "whenever" desired.

It is suggested that Applicant may wish to consider further review of any test data disclosed or evidence thereafter (e.g. via 1.132 Declaration) as to the metes and bounds of some specific amount/timeline regimen of both agents, that led Applicant's to believe they had stumbled upon a better combination therapy for those suffering from MS. Beyond the effect that would be expected by both known agents for their therapeutic benefit in MS sufferers, including beyond a mere synergistic effect.

The rejection is repeated below for continuity of record:

Szabo et al. teach "administering one or more additional agents for treating symptoms associated with multiple sclerosis") of glatiramer acetate and mitoxantrone (claim 11, as two of only five specifically contemplated "additional agents" also capable of treating multiple sclerosis) (see entire document, especially claims 10-11).

Arnon et al. teach the use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (see entire document, especially claims 1 and 8; col. 1, lines 35-41; and Fig. 8).

Kerwar et al. teach the use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (see entire document especially claim; col. 1; lines 5-9).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a combination composition comprising the active agents glatiramer acetate and mitoxantrone for the treatment of a subject afflicted with multiple sclerosis, in Szabo et al. because SZABO et al. teach administration of the combination (claim 10, i.e. “administering one or more additional agents for treating symptoms associated with multiple sclerosis”) of glatiramer acetate and mitoxantrone (claim 11, as two of only five specifically contemplated “additional agents” also capable of treating multiple sclerosis). ARNON et al. teach the use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (claims 1 and 8, col. 1, lines 35-41, and Fig. 8). KERWAR et al. teach the use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (claims, col. 1, lines 5-9). Based on the combination of references, it would have been predictable to one of ordinary skill in the art, at the time of the invention, to effectively administer the exclusive combination of glatiramer acetate and mitoxantrone, as primary agents (rather than only additional/secondary agents) for the treatment of multiple sclerosis in SZABO et al., because ARNON et al. teach the advantageous use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis and KERWAR et al. teach the advantageous use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

II. Advisory Action & Previous Interview:

However, the Examiner also visits the substantive arguments in regards to the unamended claims, in order to advance prosecution, should Applicant consider the filing of an RCE/continuation application.

Under the broadest reasonable interpretation of the claims, the invention as claimed is not actually drawn to a combination, but rather administering A and then B PERIODICALLY, or vice versa (glatiramer acetate and mitoxantrone), which is not necessarily together (where there systemic amounts individually or collectively treat some 'symptom' of MS). Thus, any MS regimen - since often such is by trial & error - of administering at some point A and at some point B, or vice versa (e.g. periodically), reads on the invention as claimed.

Applicant may wish to consider in the future positively claiming both:

1. That A and B are co-administered or simultaneously administered; AND
 2. The only symptom discussed by argument as providing unexpected results based on THIS combination (beyond those symptoms A & B are recognized as treating individually)...A METHOD OF REDUCING THE NUMBER OF Gd-ENHANCING LESIONS (to a subject in need thereof, by co-administering A + B) (see page 3 of last response as to Applicant's discussion of unexpected results).
- IF support is present in the specification, as relied upon in Applicant's later publication of results; in order to remove the presently maintained *In re Kerkhoven* fact pattern grounds of rejection under 35 USC 103.

In summary, Applicant's request for reconsideration and reliance upon various prior art references/opinions within the art (Exhibits), have been fully considered but are not found persuasive.

The 35 USC 103 rejection is maintained, the combination being deemed predictable as to success in treating MS (one or more of four standard forms).

The Examiner maintains reliance upon the rationale of *In re Kerkhoven*, that it would have been obvious to combine to known drugs for their known purpose (equivalents). It is noted that:

1. Additive effects do not traverse this grounds - without more, the results Applicants has provided on page 2-3 of 68 in the response (labeled unexpected), are presently deemed additive effects; and;
2. Furthermore, even synergistic effects may be called into question, without further showing; since synergism is itself deemed unpredictable in the art..

Applicant's arguments that the FDA does not view any drug combinations as having predictable results is not deemed to obviate either of #1, or 2, above; as to the tests/case law applied in the determination of patentability. The Patent Office and the Food & Drug Administration operate under different standards, which are not necessarily applicable to the other, in the determination of patentable subject matter versus safe-for-public use foods/drugs.

2144.06 [R-6] Art Recognized Equivalence for the Same Purpose

>I. < COMBINING EQUIVALENTS KNOWN FOR THE SAME PURPOSE

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried

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detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). **

The Examiner copies the previous Interview Summary for continuity of record:

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant telephoned to discuss the outstanding 35 USC 103 rejection in the Final Rejection. Applicant's position is that the issue rests on whether the combination of art applied would have rendered the claimed invention predictable, with a reasonable expectation of success.

The prior art does not teach using the specific combination of known MS drugs, for their known purpose:

1. The 1st compound Glatiramer acetate is well known in MS therapy (reference of record);
2. The 2nd compound, Mitoxantrone, the Kerwar reference teaches or suggests for use for treating MS, alone. Applicant indicates that, as for MS combinations, they have filed 1 reference casting doubt on the predictability of combinations - at least as to additive effect (e.g. the combination had no greater effect). The Examiner indicated that the test for obviousness for using two known compounds for their known use, is not whether the art has shown something less than a synergistic effect (which in itself by testing, may not be enough to even overcome an obviousness rejection).
- I. Applicant then indicated they are submitting 2 new references that show even reduced effect with combinations of known MS drugs. Applicant's position being that they have rebutted the prima facie case and that unpredictability is present.
- II. Secondly, Applicant reiterated the FDA's position, that they made of record, that combinations of known drugs for their known uses are 'generally' unpredictable under FDA guidelines. The Examiner indicated the USPTO follows separate guidelines [e.g. *In re Kerkhoven*] from the FDA; but that the relevance of this statement in the context of the other evidence will be fully reviewed.
- III. Thirdly, and most importantly the Examiner noted, Applicant will be reviewing the test data from this combination to determine if in fact a synergistic, as opposed to merely additive, effect was shown by this combination. Applicant will be filing the response with the above shortly, which will be fully considered by the Examiner.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960.

The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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MA, 4/11/10

/Maury Audet/
Primary Examiner, Art Unit 1654